Synthesis of a Multifunctional Gibberellin Synthon

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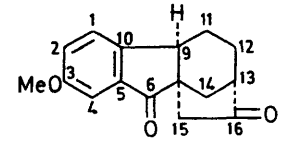
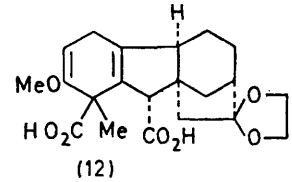
Summary An efficient stereospecific synthesis of 16, 16-ethylenedioxy-3-methoxy-9α*H*-gibba-A-triene-4,6α-dicarboxylic acid suitable for elaboration to gibberellin A_4 is described.

THE synthetic challenge offered by the structural complexity of the gibberellins has attracted the attention of a number of research groups to this problem. We report here a straightforward synthesis of 16,16-ethylenedioxy-3-methoxy-9α*H*-gibba-A-triene-4,6α-dicarboxylic acid (**11**) which embodies multifunctionality suitable for transformation to gibberellin A_4, by application of the ring A elaborative sequence recently described by Loewenthal.[1]

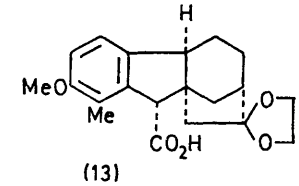
The hydroxyacetal† (**2**), m.p. 138—139°, prepared from 3-methoxy-6,16-dioxo-9α*H*-gibba-A-triene[2] (**1**) by selective acetalisation (ethylene glycol, benzene, 10h) and reduction ($LiAlH_4$, ether) was converted[3] (butylsodium, tetrahydrofuran; CO_2, ether) into the hydroxycarboxylic acid (**3**). Hydrogenolysis (methyl acetate, $HClO_4$, Pd–C) of the corresponding methyl ester (**4**), m.p. 166—167°, afforded, with concomitant deacetalisation, the keto-ester (**5**), m.p. 113—114°. Re-acetalisation of (**5**) gave the ester-acetal (**6**) from which the *N*-ethylamide (**7**), m.p. 185—186°, was derived by treatment with lithium–ethylamide in tetrahydrofuran. The overall yield of (**7**) from (**1**) was *ca.* 65%. Regiospecific carboxylation of (**7**) at C-6 was accomplished in high yield (82%) *via* the amide-benzylic dianion of (**7**) generated by treatment of (**7**) with butyl-lithium (2·5 equiv.) in tetrahydrofuran followed by carbonation (CO_2, ether) of the cherry-red solution of the dianion, and acidification. The amido-acid (**8**) thus obtained, as a single stereoisomer, was assigned the α-configuration at C-6 since its methyl ester (**9**) was not epimerised, or even equilibrated, on treatment with sodium methoxide and could be reconverted into (**8**) on hydrolysis. These findings are in keeping with the known stability towards alkali of methyl *epiallo*-gibberate[4] to which (**9**) bears a close resemblance. Since (**8**) was inert to hydrolytic conditions, conversion of (**8**) into the required diacid (**11**) was achieved (80%) by nitrosation[5] (N_2O_4, NaOAc, CH_2Cl_2) of (**9**) to give (**10**) followed by hydrolysis (5N-NaOH, MeOH; H_2SO_4) to (**11**), m.p. 207—215°.†



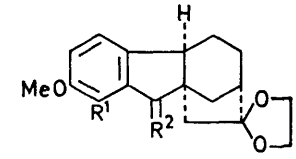
(**1**)



(**12**)



(**13**)



(**2**) $R^1 = H$, $R^2 = \alpha$-H, β-OH
(**3**) $R^1 = CO_2H$, $R^2 = \alpha$-H, β-OH
(**4**) $R^1 = CO_2Me$, $R^2 = \alpha$-H, β-OH
(**5**) $R^1 = CO_2Me$, $R^2 = H_2$ (C = O at C-16)
(**6**) $R^1 = CO_2Me$, $R^2 = H_2$
(**7**) $R^1 = CONHEt$, $R^2 = H_2$
(**8**) $R^1 = CONHEt$, $R^2 = \beta$-H, α-CO_2H
(**9**) $R^1 = CONHEt$, $R^2 = \beta$-H, α-CO_2Me
(**10**) $R^1 = CON(NO)Et$, $R^2 = \beta$-H, α-CO_2Me
(**11**) $R^1 = CO_2H$, $R^2 = \beta$-H, α-CO_2H

A preliminary investigation of further steps in the synthesis has shown that the diacid (**11**) can be converted, by Birch reduction and C-4 methylation into (**12**) (gross structure) but that (**12**) readily undergoes decarboxylation and oxidation to (**13**) under very mild conditions.

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† All new compounds gave satisfactory analytical and spectra ldata.

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